ARIC Manuscript Proposal #2908

PC Reviewed: 2/13/2018  Status: _____  Priority: 2
SC Reviewed: _________  Status: _____  Priority: _____

1.a. Full Title: Association Between the Use of Proton Pump Inhibitors and Cardiovascular Disease in the Atherosclerosis Risk In Communities (ARIC) Cohort Study

b. Abbreviated Title (Length 26 characters): PPI use and risk of CVD

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. EB

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3. Timeline:
Data analysis will start immediately. A manuscript is expected to be prepared within 10 months.

4. Rationale:
Proton pump inhibitors (PPIs) are extremely common and overused: PPIs are used for treatment of acid-related disorders such as heartburn, and are among the most commonly used drugs in the world. PPIs were used in 9.2% of outpatient visits in 2009,1 use in infants has increased 4-fold from 2000 to 2003,2 and use in children has increased 7-fold from 1997 to 2009.3 PPIs are often taken inappropriately. Notably, PPIs have not been approved by the FDA for long-term use, and one study found more than 50% of prescriptions for PPIs were prescribed improperly.4 Additionally, PPIs are now available over-the-counter, meaning that their use is often not
supervised by a health care provider. Finally, this overuse is expensive; in 2006, global expenditure on PPIs was approximately $8.6 billion.4

PPI use has been implicated as a risk factor for cardiovascular disease (CVD), but critical gaps in knowledge remain: The theory that PPIs affect cardiovascular health was formed in the context of trials of antiplatelet drugs, particularly clopidogrel. Since PPIs and clopidogrel typically compete for the same receptor, use of PPIs might impair the metabolic activation of clopidogrel.5 Indeed, most research found an increased risk of CVD among patients at high-risk of CVD who were concomitantly taking clopidogrel with a PPI, compared to clopidogrel-only users.5 However, this hypothesis was short-lived; ensuing research found that, among patients at high-risk of CVD, PPI users have an increased risk of CVD compared to nonusers regardless of clopidogrel use.5 One explanation for these findings is that PPI use negatively affects vascular health independent of clopidogrel activation. Plausible biological mechanisms exist that lend credence to this explanation. For one, PPIs increase the levels of asymmetrical dimethylarginine, a known risk factor for CVD, in a murine model and ex vivo human tissues.6 Other potential mechanisms include 1) electrolyte imbalance and 2) accelerated human endothelial senescence.5,6 Existing research, including a meta-analysis of randomized controlled trials,7 has focused on coronary heart disease;5,8 studies reported between a 16 to 70% higher risk of coronary heart disease in PPI users compared to nonusers. However, the relation of PPI use with incident total CVD and its other major components – stroke and heart failure – remains unknown in the general population.

Current progress: Using the Rochester Epidemiology Project’s medical records-linkage system, we identified all eligible residents of Olmsted County, MN on January 1, 2004 (N=58,175), and conducted preliminary analyses. After adjustment for age, sex, race, education, hypertension, hyperlipidemia, diabetes, and body-mass-index, PPI use was associated with an approximately 80% higher risk of CVD (hazard ratio [95% CI]: 1.80 [1.63-1.99]; 2179 CVD events) and heart failure (hazard ratio [95% CI]: 1.79 [1.41-2.28]; 352 heart failure events) compared to nonusers. Users of PPIs also had an approximately 65% greater risk of coronary heart disease (hazard ratio [95% CI]: 1.68 [1.39-2.05]; 622 coronary heart disease events) and stroke (hazard ratio [95% CI]: 1.64 [1.47-1.83]; 1922 stroke events) than nonusers. To demonstrate specificity of association, we additionally hypothesized that there is not an association between use of H2-blockers – another commonly used class of medications with similar indications as PPIs – and CVD. However, use of H2-blockers was also associated with a higher risk of CVD (adjusted hazard ratio [95% CI]: 1.29 [1.13-1.47]; 2327 CVD events). In conclusion, PPI use is associated with a higher risk of CVD, coronary heart disease, stroke and heart failure. Use of a drug with no known serious cardiac toxicity – H2-blockers – was also associated with a greater risk of CVD, warranting further study.

Next steps: Our preliminary findings suggest a significant association between PPI use and later CVD events, but the REP data have weaknesses that make it important to validate these findings in an additional cohort. The ARIC Study brings unique strengths to understanding the association between PPI use and CVD outcomes. In particular, the ARIC Study offers 1) validated cardiovascular outcomes, including stroke (the Rochester Epidemiology Project does not have validated stroke events); 2) PPI use was assessed every year in every participant starting in 2006, allowing us to model PPI use as time-varying with greater precision than with the Rochester Epidemiology Project; and 3) research-quality measurement of covariates in all participants.
5. **Hypotheses:**
   - Use of PPI at baseline is associated with incident total CVD, stroke, coronary heart disease, and heart failure, independent of known CVD risk factors.
   - To demonstrate specificity of association, we additionally hypothesize there is not an association between use of H$_2$-blockers – another commonly used class of medications with similar indications as PPIs – and CVD.

6. **Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).**

   **Study design:** ARIC visit 1 will serve as baseline. We will exclude persons who had a history of CVD, and follow the eligible cohort for incident CVD events.

   **Time-dependent exposure variable:** Since PPIs were not introduced to the US market until 1990, we will consider all PPI users at ARIC visit 1 as first-time users, as opposed to prevalent users. This new-user design will minimize selection bias.$^9$ The use of PPIs and H$_2$-blockers was measured at all ARIC visits through direct visual inspection of pill bottles for all medications used during the preceding 2 weeks. Exposure to PPIs and H$_2$-blockers was also obtained as part of the annual telephone follow-up, which included questions about medication use starting in September 2006. At each telephone follow-up from 2006 onward, participants were asked to assemble all medications they were taking and to “read the names of all the medications prescribed by a doctor.” Due to the dynamic nature of our exposure, we will use this information to create a time-varying exposure.

   **Outcome:** Incident total CVD, stroke, heart failure, and coronary heart disease after ARIC visit 1. We will define an incident CVD event as the first occurrence of 1) heart failure, 2) coronary heart disease, or 3) stroke.

   **Covariates:** Most likely confounding variables, which we will adjust for statistically, are age, sex, race, education, systolic blood pressure, blood pressure medications, hyperlipidemia, diabetes, body-mass-index, physical activity, and tobacco smoking status. We will use baseline measurements to adjust for these factors.

   **Analyses:** Baseline characteristics of participants will be compared by PPI use. For each outcome, we will compute person-years of follow-up as time elapsed from the baseline date to whichever came first: outcome of interest, loss to follow-up, death, or the end of follow-up. Thus, for CVD, the first of any of the three outcomes (stroke, heart failure, or coronary heart disease) will be the incidence date. We will use Poisson regression to calculate incidence rates for each outcome by PPI-use. Using Cox proportional hazards regression, we will compute adjusted hazard ratios of the CVD outcomes in relation to time-varying PPI use.$^{10}$

   Other analyses will include 1) matching on propensity scores to balance covariates between PPI users and nonusers,$^{11}$ 2) stratifying by various characteristics when possible to assess whether the PPI-CVD association differs by sub-group (e.g., PPI dose, duration of PPI use, clopidogrel use, age, type of PPI, sex, race, duration of follow-up); 3) restricting analyses to participants with a
diagnosis of gastroesophageal reflux disease or a self-reported history of heartburn to make PPI users and non-users more similar; 4) excluding the first year of CVD events after baseline, since we hypothesize that any effect of PPIs on vascular health would be from chronic, not acute use; and 5) using H2-blocker users as an active comparator group.

**Limitations:**

1. A main limitation is gaps in medication use ascertainment before 2006. Up until 2006, medication use was only ascertained at ARIC exams, which were conducted at roughly 3-year intervals through ARIC visit 4. ARIC V1 was during 1987-1989, V2 during 1990-1992, V3 during 1993-1995, and V4 during 1996-1998. Thus, there will be a gap in medication ascertainment between 1998 and 2006. After 2006, ARIC ascertained medication use annually. Because PPI use is more common after 2006 than before, and ARIC data will represent some of the only information on the association of PPI use with development of CVD, we believe this limitation is reasonable.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes  X No

   b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? ____ Yes  ____ No
   (This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes  X No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”? ____ Yes  ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

   X Yes  __ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?
   ARIC Manuscript Proposal #2509: Association Between the Use of Proton Pump Inhibitors and Chronic Kidney Disease in the Atherosclerosis Risk In Communities (ARIC) Cohort Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes  X No

11.b. If yes, is the proposal
A. primarily the result of an ancillary study (list number* __________)
B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ __________)

*ancillary studies are listed by number at http://www.cscs.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PubMed Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscs.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes X No.
References


